

REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 31, 32, and 39-42 are pending in this application. Claims 1-30, 33-38 have been previously canceled without prejudice. Claims 39-42 are amended. Applicant respectfully requests entry of the amendments, and remarks made herein into the file history of the application. Upon entry of the amendments, claims 31, 32 and 39-42 will be pending and under active consideration.

b. Amendment to the Claims

Claims 39 and 40 have been amended to be directed to a vector comprising a heterologous sequence, wherein the heterologous sequence consists of the nucleic acid of claim 31 or 32. Claims 41 and 42 have been amended to be directed to a probe comprising a heterologous sequence, wherein the heterologous sequence consists of the nucleic acid of claim 31 or 32. Support for claims 39-42 can be found throughout the specification, for example, paragraph 0043, which is set forth below.

Accordingly, the invention provides several substantially pure nucleic acids (e.g., genomic DNA, cDNA, or synthetic DNA) each comprising a novel GAM oligonucleotide, vector comprising the DNAs, probes comprising the DNAs, a method and system for selectively modulating translation of known target genes utilizing the vectors, and method and system utilizing the GAM probes to modulate expression of GAM target genes.

Vectors are well known to be useful for many purposes, including the transfer of a nucleic acid of interest. The nucleic acid of interest is considered to be “heterologous” with respect to the basic construct of a vector. The above provided passage of paragraph 0069 of the specification clearly shows that a vector is contemplated that includes a nucleic acid of interest such as the subject matter of claims 31 or 32. One of ordinary skill in the art would recognize that features heterologous to the nucleic acid of claim 31 or 32 would be necessary for a functional vector.

Probes are well known to be useful for purpose including the hybridization and detection of a nucleic acid of interest. Hybridization is typically accomplished by using a sequence that is sufficiently complementary to the target sequence. The hybridization sequence is considered to be “heterologous” with respect to the basic construct of a probe useful for detection. The above provided passage clearly shows that a probe is contemplated that includes a hybridization sequence, such as the subject matter of claims 31 or 32. One of ordinary skill in the art would recognized that features other than the heterologous sequence would be necessary for identifying whether the probe bound to a complementary sequence.

c. Objection to the Specification

On pages 3-5 of the Office Action, the Examiner objects to the specification's reference to Tables 1-11 at paragraph 0033 and elsewhere because Applicant is allegedly required under MPEP §608.01(p) to make a specific reference to which portions of Tables 1-11 are relied upon for support of the claimed subject matter. Applicant respectfully disagrees.

The Examiner's reference to MPEP §608.01(p) is misguided as this section is directed to incorporation of material or references from a separate U.S. patent or patent application. As shown at paragraph 0029 of the specification, the material being incorporated in Tables 1-11 was submitted pursuant to 37 C.F.R. §1.52(e) as part of the instant application as originally filed. Therefore, Tables 1-11 are a permanent record in the file of the application and are considered part of the specification. Under 37 C.F.R. §1.52(e)(5), the specification must contain an incorporation by reference of the material in a separate paragraph identifying the name of each file, their date of creation, and their size in bytes. Applicant has complied with these rules and submits that any sequence of interest can be searched by the GAM number within Tables 1-11. Because the incorporation by reference to Tables 1-11, they are part of the specification and in compliance with the Patent Rules, Applicant submits that the objection to the reference to Tables 1-11 in the specification is improper and should be withdrawn.

2. Patentability Remarks

a. 35 U.S.C. §101

On pages 4-10 of the Office Action, the Examiner rejects claims 31, 32, and 39-42 under 35 U.S.C. §101 for lacking support in the specification for credible utility. Applicant respectfully disagrees.

Specifically, Applicant asserts that the Examiner has impermissibly applied a higher evidentiary standard for establishing utility of the claimed nucleic acids. The evidentiary standard that the Patent Office should use throughout *ex parte* examination in setting forth the utility rejection is preponderance of the totality of the evidence under consideration. A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is true. *See Herman v. Huddleston*, 459 U.S. 375 (1983). To overcome the presumption of truth of Applicant's assertion of utility, the Examiner must establish by presenting countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility.

The crux of the Examiner's rejection is that although the target genes disclosed in Table 7 have specific and substantial utility based upon Applicant's algorithm, Applicant's assertion lacks credibility as it relates to the claimed miRNA nucleic acids binding and inhibiting expression of a target gene such as SERPINA or cathepsin K (CTSK). Specifically, the Examiner asserts that the prediction model taught by Applicant provides no evidence that the claimed nucleic acids function as miRNA-like molecules. The Examiner further disagrees that the miRNA bioinformation prediction programs such as those disclosed

in Bentwich *et al.*, *FEBS Letter* 579:5904-5910 (2005) and Martin *et al.*, *J. Biosci.* 32:1049-1052 (2007) has a success rate of 61-78% of the time even though its error rates are 22-39%. The Examiner's only explanation is that the state of the miRNA prediction art suggests significant false positive rates and recommends biological validation. This point is repeatedly stated by the Examiner that the function of SEQ ID NO: 15 as a functional miRNA that targets and modulates expression of a target gene (such as CTSK) must be shown experimentally and states that the experimental evidence that the claimed nucleic acids regulate the asserted target CTSK would be argumentative and requires a declaration.

A careful review of the basis of the rejection shows that the Examiner requires experimental certainty or 100% assurance that the claimed nucleic acids act or form a miRNA in order to remove any question of truth to the stated utility. Applicant submits this application of the law is impermissible.

Applicant submits that an assertion is credible unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. For example, as discussed in §2107.02 III B of the MPEP, an assertion of utility would not be considered credible where a person of ordinary skill would consider the assertion to be "incredible in view of contemporary knowledge" and where nothing offered by Applicant would counter what contemporary knowledge might otherwise suggest. Rejections under 35 U.S.C. §101 based on lack of credible utility have been sustained by federal courts when the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle or was wholly inconsistent with contemporary knowledge in the art. See *In re Gazave*, 379 F.2d 973 (CCPA 1967).

(1) Applicant's miRNA prediction Algorithm Does Not Violate Scientific Principle

In response to the Examiner's assertions and the stated law above, Applicant first asserts that the Examiner has provided no evidence to countervail that miRNA SEQ ID NO: 15 is likely to inhibit expression of the predicted targets such as CTSK. Whether or not the claimed polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Martin (cited again by Examiner on pages 9 and 10 of the Office Action) is irrelevant. The proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides may be used to modulate expression of the specific mRNA targets. Applicant submits that evidence has been presented throughout the file history of this application.

For example, paragraphs 0245-0251 of the application disclose that the mRNA targets of the claimed polynucleotides were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described in paragraphs 0027-0029 and 0245-0254 for identifying target binding sites of miRNAs is based upon studies at the time of filing demonstrating that miRNAs bind to target binding sites as disclosed in references such as Wightman *et al.* (1993),

Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all of record. Accordingly, Applicant's algorithm does not violate any scientific principle and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms.

(2) Success Rate

Perhaps most indicative of the Examiner's impermissible application of a higher evidentiary standard for establishing utility of the claimed nucleic acids is the Examiner's skepticism regarding the state of the miRNA prediction art at the time of filing. Rather than acknowledge that the Examiner's own cited algorithm from Bentwich and Martin predicted miRNA/target binding at a 61-78% success rate, the Examiner simply dismisses the programs' ability to predict list of candidate precursor and mature miRNAs, and in its place requires a 100% guarantee of a miRNA/target binding via experimental validation. Applicant respectfully submits, however, that these statements by the Examiner fail to present the required countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. Accordingly, the Examiner has failed to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. A 61-78% success rate is well over the threshold of providing 50% assurance regarding the truth of the statement of utility. Accordingly, the Examiner has failed to provide by a preponderance of the evidence that Applicant's asserted utility fails.

(3) Specific/Substantial Utility for CTSK

Lastly, on page 5 of the Office Action, the Examiner acknowledges that Table 7 finds that the claimed miRNA SEQ ID NO: 15 regulates at least four different genes, including SERPINA3 and CTSK. As discussed previously, the claimed nucleic acids are capable of binding SERPINA3 with a 18 out of 22 nucleotide complementation. Likewise, the claimed nucleic acids are capable of binding to the CTSK mRNA with 18 out of 22 nucleotide complementarity as shown in Table 7, lines 1475-1480 and shown below.

GAM NAME	GAM RNA SEQUENCE	TARGET REF-ID	UTR	TARGET REF-ID	BS-SEQ	BINDING-SITE (UPPER:GAM; LOWER:TARGET)	DRAW	POS
=====	=====	=====	---	=====	=====	=====	=====	=====
GAM1032	CTAGACTGAAG CTCCTTGAGGA	CTSK NM_000396.2	3	TCCTCAAGGTAGA	C	TGAAG TAGAC ATCTG T	- CT GA TAAA-	A CCTTGAGGA GGAAGCTCCT T

Applicant submits that Table 7 discloses that the claimed nucleic acids are of a specific and unique nature because these nucleic acids regulate the translation of mRNAs from the specific target gene CTSK. At the time of filing, it was known that the CTSK gene encodes a cysteine protease that is expressed in osteoclasts. Inui, T. *et al. J Biol Chem*, 1997;272(13):8109-12 ("Inui" hereafter) at p. 8109,

col. 2. Additionally, CTSK was known to have proteolytic activity against Type I collagen, and to play a role in osteoclastic bone resorption. *Id.* Specifically, an antisense oligodeoxynucleotide against the CTSK transcript decreased osteoclast-mediated pit formation, which is an indicator of osteoclastic bone resorption. *Id.* at p. 8110, col. 2-p. 8111, col. 1. Since osteoporosis is linked to osteoclastic bone resorption, the evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. One such benefit is the ability to modulate expression of CTSK in order to modulate osteoclastic bone resorption, such as occurs in osteoporosis. In view of the foregoing, the asserted utility of the claimed invention is not vague or meaningless, and there is well defined public benefit to regulating the CTSK gene. Therefore, Applicant asserts that the claimed nucleic acids have specific, substantial and credible utility, and requests that the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §101 for lacking utility has been overcome and therefore should be withdrawn.

b. 35 U.S.C. §112, First Paragraph (Enablement)

On page 5 of the Office Action, the Examiner maintained the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that since the claimed invention is not supported by a credible asserted utility, one skilled in the art would not know how to use the claimed invention. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the CTSK transcript, which in turn, may respectfully alter osteoclastic bone resorption. Therefore, Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §112 for lack of enablement has been overcome and therefore should be withdrawn.

c. 35 U.S.C. §103

On pages 13-20 of the Office Action, the Examiner maintains the rejection claims 31, 32, and 39-42 under 35 U.S.C. §103(a) over U.S. Patent No. 6,812,339 (“Venter”) and GenBank Accession No. AQ420078 (“Zhao”) in view of Buck *et al.* (*Biotechniques*, 1999:27(3):536-528) (“Buck”), U.S. Patent No. 5,541,308 (“Hogan”), and Brown *et al.*, *Vet. Pathol.* 35:159-167 (1998). The Examiner states on page 19 that because the claims are not limited to miRNAs or functional language related thereto, one of skill would reasonably expect the set of probes and primers complementary to the target nucleic acid sequences would all be capable of hybridizing to said sequences in the manner necessary for use a probes and primers. The Examiner concludes that although the set of sequences from Venter and Zhao are large, it is finite and unambiguously described by the target sequences. Applicant respectfully disagrees.

The Examiner has failed to address the evidence provided by Applicant in the previous response of October 1, 2008 regarding the non-obviousness of the claimed nucleic acids relating to a miRNA, or a

hairpin that is processed into a miRNA that is capable of regulating a target gene transcript in *trans*. Specifically, there is no teaching or suggestion in Venter or Zhao in view of Buck, Hogan, or Brown for identifying the claimed nucleic acids and specifically miRNAs based upon identifying miRNA/target regulation in *trans*. Amongst the millions of possible primers as discussed below, the cited references provide no guidance to one of skill of the non-obvious properties of the claimed nucleic acids. Accordingly, one of skill would not even be able to begin to narrow down the choices of designed primers or probes to identify the claimed nucleic acids and their respective target genes.

Applicant further submits that even if the primers or probes cited by the Examiner include the claimed nucleic acids of claims 31 and 32, this is not sufficient by itself to establish a *prima facie* case of obviousness. See MPEP §2144.08.II (“The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness”). Considering the massive size of the number of Venter or Zhao sequences in view of Buck, Hogan, or Brown, there is simply no way for one of skill to envisage the claimed subgenus of nucleic acids within the genus. See MPEP §2144.08.a.4(a).

As argued in Applicant’s response of October 1, 2008, there are at least 39,448,389 different sequences encompassed by the group of 18-131 nucleotide-long primers as taught in Buck that are capable of binding anywhere along the sequence of Venter. There are 12,458,898 different sequence encompassed by the group of 15-50 nucleotide-long probes as taught by Hogan that are capable of binding anywhere along the Venter sequence.¹

Similarly, there are at least 69,597 different sequences encompassed by the group of 18-131 nucleotide-long primers as taught in Buck that are capable of binding anywhere along the sequence of Zhao. There are 23,490 different sequence encompassed by the group of 15-50 nucleotide-long probes as taught by Hogan that are capable of binding anywhere along the Zhao sequence.²

The group of claimed nucleic acids related to SEQ ID NOS: 15 and 6527 is but one subgenus within the massive genus of primers or probes. Again, against this huge number of choices, there is no teaching or suggestion in the Venter or Zhao sequences in view of Buck, Hogan or Brown to lead one of skill to select the claimed nucleic acids related to a miRNA, or a hairpin that is processed into a miRNA that is capable of regulating a gene transcript in *trans*, as is provided in the instant claims. The same holds true for vector and probes as provided in claims 39-42—there is nothing in any of the art cited by the Examiner to lead one of skill to select a probe related to SEQ ID NO: 15 or SEQ ID NO:6527 from

¹ Accounting for sequences that can have as little as 60% complementarity to the sequence of Venter increases the massive number of possible sequences to an essentially limitless amount.

² Accounting for sequences that can have as little as 60% complementarity to the sequence of Zhao increases the massive number of possible sequences to an essentially limitless amount.

among the many millions of possible sequences taught by Venter or Zhao in view of Buck, Hogan or Brown. In view of the foregoing remarks, Applicant respectfully requests that the Examiner reconsider and withdrawn the rejection of claims 14, 30, 34, and 35 under 35 U.S.C. §103(a).

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHUGHART PC

Dated: May 15, 2009

On behalf of: Teddy C. Scott, Jr., Ph.D.
Registration No. 53,573

By: /Paul A. Jenny/
Paul A. Jenny
Registration No. 59014
Customer No. 37808

POLSINELLI SHUGHART PC
180 N. Stetson Ave., Suite 4525
Chicago, IL 60601
312.819.1900 (main)
312.873.2913 (E-fax)
312.873.3613 (direct)